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EXAMINER	
NISSEN S	
ART UNIT	**PAPER NUMBER**
1805	9

DATE MAILED: 12/10/93

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 8/16/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three month(s), ~~days~~ from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-9 are pending in the application.
   Of the above, claims 7 ~~are~~ is withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-6 and 8-9 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☒ Other

Applicants are respectfully requested to provide copies of the references in the 4/23/93 IDS as said references are no longer present in the parent case. For this reason, the IDS and 1449 has not been considered.

EXAMINER'S ACTION

III. DETAILED ACTION

15. Applicant's election with traverse of Group I, claims 1-6 and 8-9 in Paper No. 8, filed 8/16/93 is acknowledged. The traversal is on the ground(s) that the two receptor proteins do not represent two cytokines. Applicants conclude that the consideration of the synergy is in error. This is not found persuasive because even though the antagonists used in the pending claims are not cytokines. The effect of one or both of the antagonists on the effect of the two corresponding ligands would require consideration of the effect those ligands have. Since the administration of the cytokine ligands has a synergistic effect, the administration of the antagonists may also have unexpected repercussions. In addition, the reasons for restriction set forth a structural reasons for restriction as well. Accordingly, applicant's traversal does not address the argument made in the restriction requirement set forth in the restriction requirement mailed 7/27/93.

The requirement is still deemed proper and is therefore made FINAL.

16. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately describe and failing to adequately teach how to make and/or use the instant invention.

The specification recites the following on page 3 at line 14.

> "soluble TNFR molecules include, for example, analogs or subunits of native proteins having at least 20 amino acids and h which exhibit at least some biological activity in common with TNFRI, TNFRII, or TNF binding proteins....Equivalent soluble TNFRs include polypeptides which vary from these sequences by one or more substitutions, deletions, or additions and which retain the ability to bind TNF or inhibit TNF signal transduction activity via cell surface bound TNF receptor proteins....".

The specification goes on to refer to proteins having "sufficient homology" without really providing the routineer with an exact definition of how such homology is to be determined. Without such

guidance, undue experimentation would be required to determine which of the "substantially homologous" proteins fall within applicant's disclosure.

Review of Figures 3 and 4 of the data of Table B does not indicate that the F_c /TNFr fusions are statistically significant when compared with saline. Note that figuring the standard deviation into the data reveals that the figures could be the same. Similar results are shown in Tables C and D. Note that Table D shows the same severity score for the TNFr/F_c as PBS. The day of onset is only accurate to +/- 6 days. That is not accurate to really show that the F_c postpones the onset of arthritis in rats. The data in figures 3 and 4 show similar results. Accordingly, applicants have not really provided data which supports their claims that the F_c/TNFr fusions alone provide treatment for arthritis.

17. Claims 1-6 and 8-9 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

18. 35 U.S.C. § 101 reads as follows:
"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

19. Claims 1-6 and 8-9 are rejected under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks utility.

This rejection is essentially being made for the reasons argued in the paragraph immediately above. The data presented in the specification is not accurate enough to really show a reduction in joint diameter. Furthermore, the reduction is not shown to actually improve the condition of the patient. The applicants have no comparison to normal condition to show that the reduction of joint swelling of @0.25mm (fig. 3) is really clinically meaningful. In addition, the data in the Tables A-D does not show that the F_c/TNFr fusion is effective when administered alone. The only apparent effective combination seems to be the combination with the IL1r. Applicants must provide a showing that the disclosed results are statistically and clinically relevant.

20. Claims 1-6 and 8-9 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility. The claims are also rejected under §112, first paragraph as failing to teach how to make and/or use the instant invention.

The invention claims the use of recombinant human TNFr to treat arthritis. Such a treatment is inherently an in vivo environment. The dependent claims recite the use of the therapy in humans. To support such claims, applicants have data from rats. The use of rat data to support human claims is not sufficient. To begin with, it is unclear that the routineer would genuinely be motivated to treat arthritic rats. So, the only real use of the claimed method would have to be in humans. However, the generalization from rats to humans is not realistic absent concrete evidence to the contrary. The anatomical differences between the two mammals would render the extrapolation of rodent data to humans unpredictable. Furthermore, rodents are known to often be susceptible to different diseases than humans which would indicate different immune systems. Accordingly, applicants are invited to present clinical trials or persuasive evidence that rats are an art recognized equivalent for humans in the study of arthritis. To support this assertion, the Bloom reference is made of record. Note specifically that line 9 of the second paragraph, right column states that different results were obtained in mice and the "administration of IFNΓ,known to be critical to protection, was not able to induce a cure.". While this reference deals with cytokines, not so much the antagonists of the claimed invention, the admonition of the first paragraph and the foregoing recitation is considered relevant nontheless. The targets of the claimed method is the cytokines discussed by Bloom and therefore any method of treatment would have to accomadate the limitations inherent in cytokine therapy as well. Accordingly, the instant invention is considered to lack utility.

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. Claims 1-3 are rejected under 35 U.S.C. § 102(b) as being anticipated by Brennan et al.

The claims recite the use of a TNF antagonist in the mediation of TNF associated arthritis. The claims are not limited to the type of antagonist.

The Brennan reference teaches the inhibition of IL1 production in explanted synovial cell cultures from arthritic human patients. The reduction in the production of IL1 is consistent with the reduction in bone damage and cartilidge destruction associated

with rheumatoid arthritis. Note that the reference teaches on pg. 244 first paragraph, "...intra-articular IL1 can induce arthritis.". Therefore, since the source of the synovial cell culture is the human patient, the reference anticipates the rejected claims.

23. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

24. Claims 4-5 and 8-9 are rejected under 35 U.S.C. § 103 as being unpatentable over Brennan and Harris in view of Smith.

The claims recite the following limitations.

> A method of treating TNF mediated arthritis with the TNFr of the preferred embodiments.

The Brennan reference has been discussed in paragraph 18 of the §102 rejection. The reference is used as a teaching of expectation of the success because the reference explicitly states that IL1 can induce arthritis and that TNF α inhibitors

can reduce the production of IL1. The Brennan reference does not teach the use of TNF receptors. However, this is not considered significant because the TNF receptors of the instant claims and anti-TNF antibodies of the operate by the same mechanism. That mechanism is the binding of TNF so that the TNF molecule cannot interact with other receptors, etc.. Therefore, one of ordinary skill in the art would have known that as long as TNF is removed from the environment, the condition of rheumatoid patients would improve.

The Harris reference teaches the use of cytokine inhibitors for the treatment of rheumatoid arthritis on page 1286, end of the 5th paragraph. Therefore, this reference is sufficient to provide the motivation to use the cytokine inhibitors of the instant invention.

The Smith reference provides the necessary teachings of the sequence of the p80TNFr which was used by applicants in the instant application. The use of such a receptor in the claimed method would have been obvious in view of the cited art set forth above.

The combination of the TNFr of Smith in the methods of therapy set forth in Harris and Brennan references would have been obvious to one of ordinary skill in the art absent evidence to the contrary. The reason for such a conclusion stems from the following disclosures. Because the prior art teaches that an antagonist to TNF will prevent the cause of arthritis (Brennan) and the art recognizes that the claimed compounds were an alternative antagonist to the antibodies of Brennan (see Harris), the routineer would merely substitute the TNFr of Smith for the antibodies of Brennan as taught by Harris to obtain the claimed invention. Therefore, applicant's claimed invention is clearly prima facie obvious absent evidence to the contrary.

The last two claims recite specific dosage amounts and times. However, the dosages are so broad as to represent merely upper and lower extremes. In other words, given the fact that the claimed dose appears to be almost 20 times as strong as that used in the representative examples, the claimed doses are probably toxic. Therefore, absent some clinical significance they are deemed to be obvious in view of the art.

25. Claim 6 is rejected under 35 U.S.C. § 103 as being unpatentable over Brennan and Harris in view of Capon and Hoogenboom in further view of Smith.

The rejected claim recites the use of a fusion F_c region with the TNFr protein.

The Brennan, Harris, and Smith references have been discussed above.

The Capon and Hoogenboom references are added to render the addition of the F_c region to the cytokine receptor (TNFr). The Capon reference teaches generically, the addition of various receptors and soluble derivatives of these receptors to N-terminus of the F_c region. Moreover, the Capon reference teaches the advantages of using such things in the addition of F_c regions for drugs which interrupt ligand and binding partner interactions. See col 4, lines 16 and following. This is exactly what applicants are claiming. The claimed TNFr is a binding partner that is used to antagonize the interaction TNF (ligand) and the cell bound receptor (binding partner). The patent teaches that the addition of the F_c region increases serum half life (see line 40 of col. 4). The Capon reference does not explicitly mention cytokines. That is why the Hoogenboom reference has been used. The Hoogenboom reference teaches the fusion of the TNFr ligand (TNF) to an immunoglobulin F_c region. Therefore, all one of ordinary skill would have to do is substitute the binding partner for the ligand as explicitly recommended by Capon. Accordingly, because Capon teaches the fusion of F_c with ligand antagonists (binding partners) and the Hoogenboom reference teaches the use of such fusions with the TNF/TNFr ligand/antagonist (binding partner) pair, it would have been obvious to one of ordinary skill in the art to perform the fusions of Capon and Hoogenboom on the molecules of Smith with the methods of Brennan and Harris.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Nisbet whose telephone number is (703) 308-4204. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TMN
November 1, 1993

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
11/1/93